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Neoadjuvant crizotinib in ALK-rearranged inflammatory myofibroblastic tumor of the urinary bladder: A case report

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ABSTRACT

INTRODUCTION: Inflammatory myofibroblastic tumor (IMT) is a rare mesenchymal tumor that involves various organs, but has a predilection for the urinary bladder in the genitourinary tract. Given that approximately half of all IMT cases have anaplastic lymphoma kinase (ALK) rearrangements, the ALK inhibitor crizotinib is suggested as a promising treatment for unresectable cases. No reports on neoadjuvant crizotinib therapy for locally advanced IMT of the bladder are available.

PRESENTATION OF CASE: We report a case of a 17-year-old Japanese boy referred to our institution for painful urination and increased urinary frequency. He was diagnosed with ALK-positive IMT via transurethral resection of the bladder tumor. Computed tomography (CT) revealed a 5-cm mass and extramural invasion at the bladder dome. The diagnosis was locally advanced IMT of the bladder. We decided that partial cystectomy can be performed if neoadjuvant crizotinib therapy reduced the tumor size. After 2 months of administration, CT showed that the longest tumor diameter was reduced by 48%. Thus, we performed partial cystectomy, and the surgical margin was negative. No recurrence developed for over 1 year.

DISCUSSION: IMT has intermediate malignant potential because its clinical course is relatively indolent with low risk of distant metastasis. As this patient is young and IMT of the bladder has good prognosis after surgical resection, bladder-preserving surgery is the most preferred approach.

CONCLUSION: Neoadjuvant crizotinib therapy may be effective for large, locally advanced, and difficult to resect tumors.

1. Introduction

Inflammatory myofibroblastic tumor (IMT) is a rare mesenchymal tumor that has intermediate malignant potential. It arises from various organs, such as the lung, retroperitoneum, and pelvis [1]. Surgical resection is the primary treatment for IMT, but unresectable cases have limited response to steroids, non-steroidal anti-inflammatory drugs (NSAIDs), radiotherapy, and chemotherapy [2–4]. A total of 50% of IMTs have anaplastic lymphoma kinase (ALK) rearrangement and overexpress ALK protein [5]. The ALK inhibitor crizotinib is effective for unresectable cases [6]. IMTs of the genitourinary tract frequently develop in the urinary bladder [7]. Transurethral resection of bladder tumor (TURBT) is often performed for pathological examination, and additional TURBT or partial cystectomy for radical resection is selected according to histologic outcomes [8]. Currently, no reports on neoadjuvant crizotinib therapy for locally advanced IMT of the bladder are available. Herein, we report a case of IMT that was successfully treated with partial cystectomy following neoadjuvant crizotinib therapy.

This work has been reported in line with the SCARE criteria [9].

2. Case presentation

A 17-year-old boy, presenting with a 2-week history of painful urination and increased urinary frequency, was referred to the first clinic. Computed tomography (CT) scan revealed an enhanced mass measuring 5 cm in diameter at the dome of the urinary bladder. Magnetic resonance imaging showed extramural invasion of the bladder, and the left ischial bone and right humerus presented high intensity on T2-weighted images and diffusion-weighted images (see Fig. 1). Thus, bone metastases was suspected. Cystoscopy demonstrated locally thickened and edematous mucosa from the posterior wall to the bladder dome. TURBT was performed for pathologic evaluation. The histological findings and

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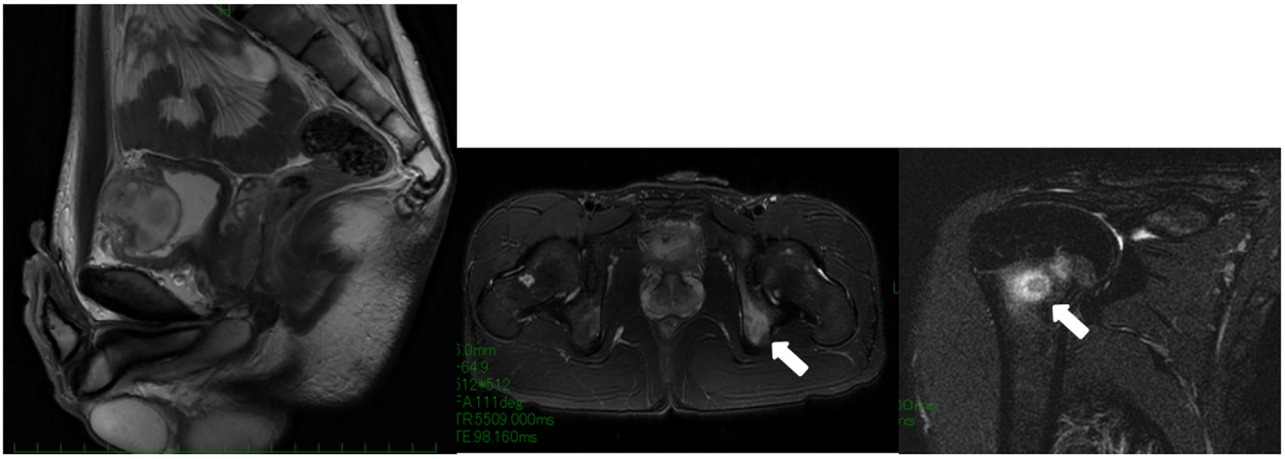

Fig. 1. *Left*, Sagittal T2-weighted MRI showed a mass measuring 5 cm in diameter at the urinary bladder dome with extramural invasion. *Middle*, The left ischial bone presented high intensity on axial T2-weighted image. *Right*, Coronal T2-weighted imaging showed local high-intensity area in the right humerus.

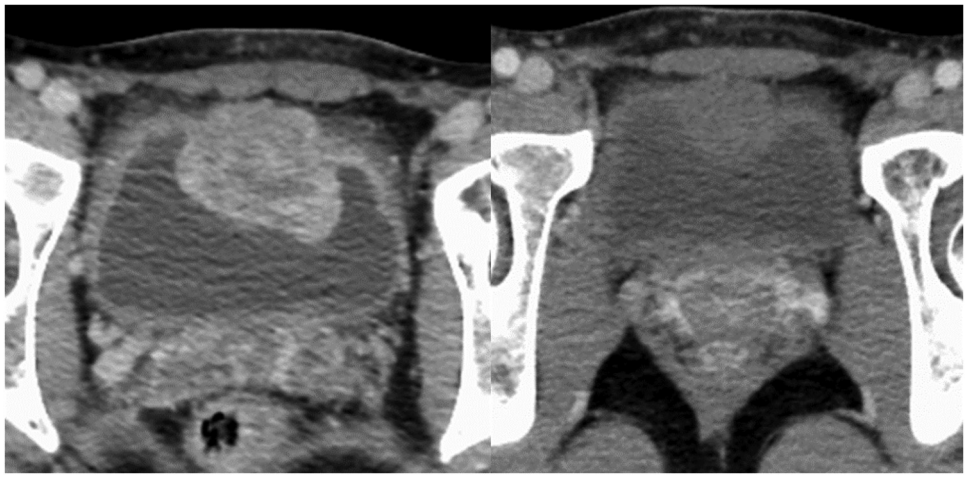

Fig. 2. *Left*, Before treatment, CT showed a mass measuring 49 mm in diameter. *Right*, After treatment, the tumor size reduced to 25 mm.

immunohistochemical staining indicated ALK-rearranged IMT. Combined ^{18}F-fluorodeoxyglucose positive-emission tomography and CT revealed hypermetabolic masses in the left ischial bone and right humerus. Therefore, he was referred to our hospital because rapid progression with distant metastases was suspected. Ischial bone biopsy was performed, and the results showed chronic inflammation but no malignant tumor. Accordingly, the patient was diagnosed with locally advanced IMT of the urinary bladder. Although we initially considered radical cystectomy for curative treatment, we decided that partial cystectomy can be performed instead if the tumor size was reduced with neoadjuvant crizotinib therapy. Thus, crizotinib was started at a dose of 250 mg twice daily. After 2 months, CT images showed a 48% reduction in the sum of the longest diameter (see Fig. 2). Adverse events were mild nausea and overlapping shadows, and no hematologic events occurred. The overlapping shadows were treated. Cystoscopy showed a nodular tumor at the bladder dome (see Fig. 3); thus, we decided that we could resect the tumor with enough surgical margin and preserve adequate capacity of the bladder after surgery. Partial cystectomy was performed. Histological examination demonstrated intersecting fascicles of spindle cell proliferation admixed with a few inflammatory cells within a myxoid stroma (see Fig. 4). Although no necrotic cells were seen, a hyalinizing area was recognized. We suspected the change as a form of therapeutic response. Immunohistochemical staining showed that the spindle cells were positive for ALK (5A4, Abcam, Cambridge, UK), and fluorescence in situ hybridization using a break-apart probe (Vysis ALK Break Apart FISH Probe Kit, Abbott Molecular, Abbott Park, IL) showed ALK rearrangement (see Fig. 5). These findings were characteristic of ALK-rearranged IMT. The patient's urination remained unchanged after surgery, and no local recurrence and distant metastases were observed 1 year after treatment.

3. Discussion

Although IMT occurs over a wide age range, it has been mostly reported in adolescent patients [10]. IMT has a relatively good prognosis and is considered to be a tumor with intermediate biologic potential because of its low risk of distant metastases [11]. On one hand, IMTs of the bladder have a local tumor recurrence rate after surgery of only 4%, and no patients with distant metastases have been reported [8]. On the other hand, IMT arising from other organs sometimes has poor prognosis because of the high rate of recurrent local relapse or distant metastases.

Surgical resection is the main therapeutic strategy for localized IMT. Most patients with IMT of the bladder undergo TURBT for pathologic evaluation and treatment. After diagnosis of IMT, cases with no residual tumor may not require further treatment, while a second TURBT or partial cystectomy may be performed for complete resection in other cases. A study that reviewed 120 cases of

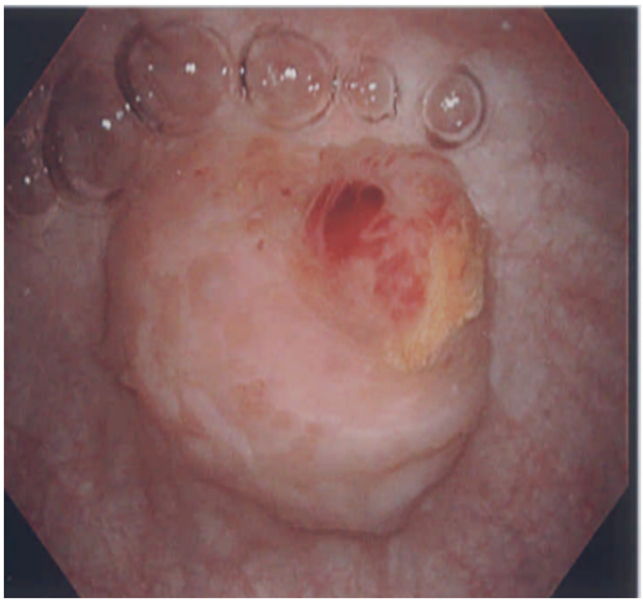

Fig. 3. Cystoscopy; a nodular tumor at the bladder dome.

IMT of the bladder reported that the primary treatment for this tumor is TURBT (60.8%), followed by partial cystectomy (29.2%), and radical cystectomy (9.2%) [8]. Among the patients treated with TURBT, 24.7% had further treatment, including partial cystectomy (17.8%), second TURBT (5.5%), and radical cystectomy (1.4%).

For unresectable cases, no standard therapeutic strategy has been established. Evidence on the efficacy of chemotherapy for unresectable cases is limited, and most reports are based on pediatric cases. Treatment regimens are likely to be selected according to the presence of soft tissue sarcoma, but the ESMO/European Sarcoma Network Working Group guidelines recommend a single dose of doxorubicin as the first choice of treatment [12–14]. If the patient has good performance status, combination chemotherapy of doxorubicin and ifosfamide every 3–4 weeks (AI therapy) is administered with the aim of favorable response.

EML4-ALK is the most common fusion gene in non-small-cell lung carcinoma (NSCLC) [15]. The ALK inhibitor crizotinib is a promising treatment for ALK-positive NSCLC and has been used in Japan since 2012. Although the prevalence of ALK rearrangements in NSCLC is only approximately 5% [15], the efficacy of crizotinib as compared with first-line chemotherapy is striking. Progression-free survival was significantly longer with crizotinib than with chemotherapy (median, 10.9 months vs. 7.0 months, $p < 0.001$), and the objective response rates were 74% and 45%, respectively ($p < 0.001$) [16]. However, unlike in NSCLC, evidence on the efficacy of crizotinib in IMT is limited.

A patient with unresectable IMT of the peritoneum received crizotinib in a phase 1 trial in 2010 [6]. The patient with ALK-rearranged IMT was administered 200 mg of crizotinib twice daily. After 3 months, tumor size reduced by 53%, and the patient achieved complete radiographic remission for 1 year and 7 months. Adverse events were edema in the extremities, joint aches, hypocalcemia, hypophosphatemia, leukopenia, and anemia, all of which were classified as grade 1. Furthermore, some case reports on

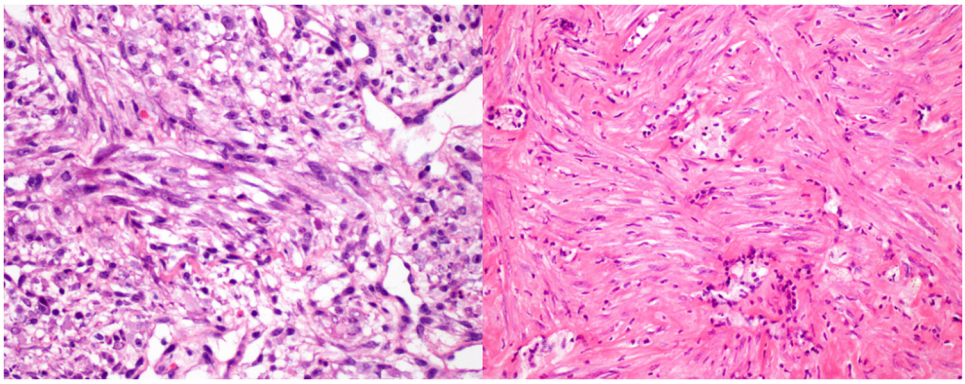

Fig. 4. *Left*, Fascicular proliferation of monotonous spindle cells within myxoid stroma. *Right*, A hyalinised area was focally present, which may indicate changes associated with crizotinib therapy.

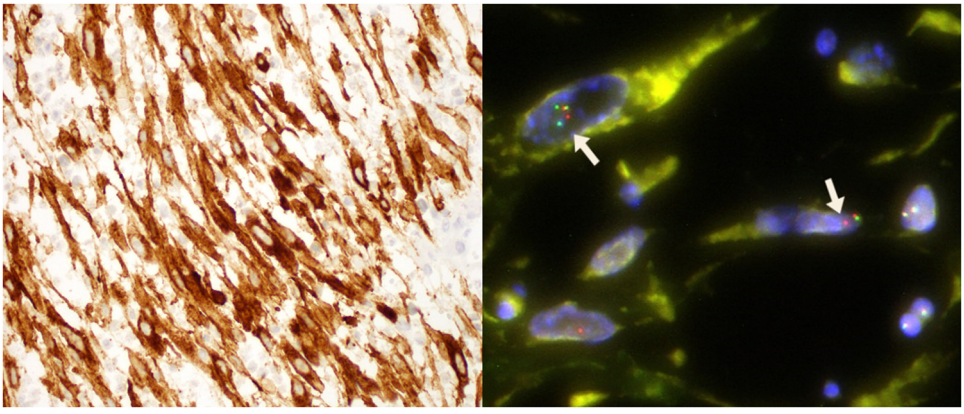

Fig. 5. *Left*, Immunohistochemical staining showed that the tumor cells were positive for ALK. *Right*, FISH showed positive evidence of *ALK* rearrangement (arrows indicate rearranged *ALK* signals).

metastatic IMTs described successful results of the other ALK inhibitors alectinib and ceritinib [17,18]. However, reports on the efficacy of ALK for IMT are limited to date, and further investigation on how to optimally use these inhibitors is needed.

Although this case was resectable at the time of diagnosis, we thought that partial cystectomy as a limited operation was better than radical cystectomy to preserve bladder capacity and quality of life (QOL) after surgery. Thus, we treated the patient with crizotinib as a neoadjuvant therapy. In young patients like this case, neoadjuvant therapy is important because QOL after cystectomy is significantly different after limited operation.

Currently, no reports regarding limited surgery with neoadjuvant crizotinib therapy for IMT of the bladder have been published. Crizotinib is well-tolerated and is a promising treatment for IMT with ALK rearrangements. Furthermore, it may be effective in cases of large or locally advanced tumors.

Conflicts of interest

We declare no conflicts of interest.

Sources of funding

Nothing to declare.

Ethical approval

No ethical approval was needed for this case study in our institution.

Consent

The patient consented for publication of the case report.

Author contribution

Yoshiyuki Nagumo: study concept, data collection, writing the paper.

Aiko Maejima: study concept, review and correct the manuscript.

Yuta Toyoshima: review and correct the manuscript.

Motokiyo Komiyama: review and correct the manuscript.

Kan Yonemori: review and correct the manuscript.

Akihiko Yoshida: data interpretation, review and correct the manuscript.

Hiroyuki Fujimoto: review and correct the manuscript.

Registration of research studies

UIN is research registry 3685.

Guarantor

Aiko Maejima and Hiroyuki Fujimoto.

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